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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHAFER, SHULAMITH H	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 02/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/918,589	HALBLEIB ET AL.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-20,22 and 24-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-20,22,24-25,30-35* is/are rejected.

7)☒ Claim(s) *26-29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647. The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Shulamith H. Shafer, Art Unit 1647.

Applicants' response of 16 December 2005 to Office action of 16 August 2005 has been entered. Applicants have cancelled claims 16 and 17, amended claims 18-20, 22, 24 and 25 and added claims 32-35. These have all been made of record.

Claims 18-20, 22, 24-35 are pending and are under examination.

Claim Rejections, Withdrawn

The rejection of claims 16 and 17 under 35 USC 103(a) as being unpatentable over US Patent 5,876,946 in view of US Patent 6,248,520 and further in view of US Patent 6,054,295 have been rendered moot by cancellation of the claims and is thus withdrawn.

The rejections of claims 18-20, 22, and 24-31 under 35 USC 103(a) as being unpatentable over US Patent 5,876,946 in view of US Patent 6,248,520 and further in view of US Patent 6,054,295 have been withdrawn upon further consideration and in view of Applicants' arguments.

New issues are set forth below.

New Grounds for Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18, 24, 25, 32-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bolger et al. (1998, WO 98/05962) in view of Roeder et al (2001, US Patent No. 6,248,520, filed 6 July 1998) and further in view of Burbaum et al (1999, US Patent No. 5,876,946). The claims of the instant invention recite a method identifying test compounds that modulate the binding of a steroid hormone receptor to a steroid hormone ligand. The independent claim of the instant invention (claim 32) recites a method of monitoring a binding interaction of a steroid hormone receptor with a fluorescently-labeled ligand in the presence of a test compound by measuring fluorescence polarization. Claim 33 recites measuring the fluorescence polarization of a mixture of a steroid hormone receptor and a fluorescently-labeled ligand; claim 34 discloses comparing the fluorescence polarization of the two mixtures.

Bolger et al teach a method for measuring competitive binding activity of molecules to steroid hormone receptors, comprising: (1) mixing a fluorescence-emitting compound that binds to the steroid hormone receptors in a solution containing the steroid hormone receptors; (2) measuring the florescence polarization of the solution; (3) incubating the solution with at least one molecule that may compete with the compound for interaction with the steroid receptors; (4) measuring the fluorescence polarization of the solution of step (3); and (5) comparing the fluorescence polarization measurements to quantify any competitive interaction (page 4, lines 13-20). Bolger also teaches a "fluormone", a shortened term for "fluorescent hormone". The reference defines fluormone as "any molecule covered by the hormone definition and emits fluorescence" (page 7, lines 14-15). This could be interpreted to encompass a hormone with a fluorescent moiety attached to it. Bolger et al does not teach a steroid hormone receptor selected from the group consisting of an androgen receptor (AR), a glucocorticoid receptor (GR) and a progesterone receptor (PR), the fluorescent label conjugated to the steroid hormone via a ligand, and a fluorescent receptor ligand selected from the group consisting of fluorescein, fluoresceinamine, DTAF, Texas Red, BODIPY dyes, Alexa dyes, tetramethylrhodamine (TMR), and conjugatable derivatives thereof. Roeder et al ('520) teach a method of screening agents that antagonize nuclear hormone receptor functioning. Among the nuclear hormone receptors that can be used in the assay system for screening potential drugs are the progesterone receptor, androgen receptor and glucocorticoid receptor (column 12, lines 53-67, bridging column 13, lines 1-8). Burbaum et al ('946) teach a high throughput screening assay, using compounds found in combinatorial libraries to determine active drug candidates. Inhibition or binding by the library compounds causes a change in the amount of an optically detectable label (abstract and column 3, lines 37-40). The reference teaches fluorescently-labelled ligands displaced by library compounds(Figure 1C and column 4, line 67, bridging column 5, line 1); the label can be attached to a ligand which binds to a receptor (column 8, lines 48-50). Burbaum et al also teach that fluorescent labels suitable for use in the invention are well known and include fluorescein, rhodamine and Texas Red (column 8, lines 62-65). The '946 patent further

discloses that nuclear receptors, such as steroid receptors, are advantageously expressed recombinantly and employed in an embodiment of this assay (column 7, lines 11-14). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to ultilize the nuclear hormone receptors taught by Roeder et al, i.e. the progesterone, androgen or glucocorticoid receptor, in the method of measuring competitive binding activity of molecules to steroid hormone receptors taught by Bolger et al, including the fluorescently-labelled ligands disclosed by Burbaum et al in the reaction mixture. The person of ordinary skill in the art would have been motivated to make these modifications because the art teaches that steroid receptors belong to a highly conserved family of receptors, the nuclear receptor superfamily. Nuclear receptors share a common structural organization, including common functional domains. These domains include a well-conserved DNA binding domain, a less well-conserved hinge area, and the C-terminal ligand binding domain. Homologous domains present in these receptor proteins serve similar roles in each. The differences observed in the ligand binding domain results in the diversity and specificity of the hormonal response. Furthermore, Bolger et al teach that the disclosed assay is a method for measuring competitive binding activity of molecules to steroid hormone receptors (page 4, lines 12-13) and discloses the use of a fluormone or "fluorescent hormone" in the disclosed method. One would reasonably expect success because Bolger et al teach the success of this method utilizing steroid receptors.

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bolger et al. (1998, WO 98/05962) in view of Roeder et al (2001, US Patent No. 6,248,520, filed 6 July 1998) and Burbaum et al (1999, US Patent No. 5,876,946) and further in view of Chen (2000, US Patent No. 6,054,295). The teachings of Bolger et al and the '520 and '946 patents are discussed above. Bolger et al. do not teach a ligand binding domain of a steroid hormone receptor fused to an N-terminal domain selected from the group consisting of glutathione-S-transferase (GST), maltose binding protein (MBP) and thioredoxin (TRX). Chen ('295) teaches constructs expressing fusion proteins of both full length nuclear receptors fused to GST, as well as ligand binding domains of nuclear hormone receptors fused to GST (column 14, lines 6-19). The patent discloses that

these fusion proteins are useful in assays to identify compounds which modulate wild-type nuclear receptor activity (column 14, lines 6-10). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to ultilize the fusion proteins of nuclear receptors fused to GST taught by the '295 reference in the method of measuring competitive binding activity of molecules to steroid hormone receptors taught by Bolger et al, including the fluorescently-labelled ligands disclosed by Burbaum et al in the reaction mixture. The person of ordinary skill in the art would have been motivated to make these modifications because Bolger et al teach that the disclosed assay is a method for measuring competitive binding activity of molecules to steroid hormone receptors (page 4, lines 12-13) and Chen teaches that fusions constructs are useful in assays to identify compounds which modulate wild-type nuclear receptor activity. One would reasonably expect success because Bolger et al teach the success of this method utilizing steroid receptors.

Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bolger et al. (1998, WO 98/05962) in view of Roeder et al (2001, US Patent No. 6,248,520, filed 6 July 1998) and Burbaum et al (1999, US Patent No. 5,876,946) and further in view of Fisher et al, (2001. Endocrinology, 4th edition, WB Saunders Co. Chapter 193, page 2604). The teachings of Bolger et al. and the '520 and '946 patents are discussed above. Bolger et al. do not teach a steroid selected from the group consisting of 5α-androstan and derivatives thereof, 4-androsten and derivatives thereof, 4-pregnen and derivatives thereof, and dexamethasone and derivatives thereof. Fisher et al teach the therapeutic use of dexamethosone as a long acting glucocorticoid (page 2604). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to ultilize the dexamethosone taught by the Fisher reference in the method of measuring competitive binding activity of molecules to steroid hormone receptors taught by Bolger et al, including the fluorescently-labelled ligands disclosed by Burbaum et al in the reaction mixture. The person of ordinary skill in the art would have been motivated to make these modifications because the use of dexamethosone as a long-acting glucocorticoid, binding to the glucocorticoid receptor, is well known in the art. One would reasonably expect success because Bolger et al teach the success of the

disclosed assay is a method for measuring competitive binding activity of molecules to steroid hormone receptors (page 4, lines 12-13).

Claims 22 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bolger et al. (1998, WO 98/05962) in view of Roeder et al (2001, US Patent No. 6,248,520, filed 6 July 1998) and Burbaum et al (1999, US Patent No. 5,876,946) and further in view of Tanaka et al (1997, Glia 20:23-37). The teachings of Bolger et al. and the '520 and '946 patents are discussed above. Bolger et al do not teach a steroid hormone receptor ligand that binds to the LBD with a K_d of less than 20 nM or a glucocorticoid receptor (GR) wherein the K_d is 0.8±0.1 nM. Tanaka et al. teach that a functional GR receptor in microglial cells binds [^{3}H]-corticosterone with a K_d of 0.8nM (page 23, abstract). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to ultilize glucocorticoid ligand that binds with high affinity to the steroid receptor taught by Tanaka et al. in the method of measuring competitive binding activity of molecules to steroid hormone receptors taught by Bolger et al, including the fluorescently-labelled ligands disclosed by Burbaum et al in the reaction mixture. The person of ordinary skill in the art would have been motivated to make these modifications because Tanaka et al. teach that corticosteroids may modulate brain functions through their actions on astrocytes and oligodendrocytes because these glial cells express GR (page 24, column 1, 2nd paragraph) and a method of modulating the hormone binding to receptor would identify a number of important processes in damaged nervous tissue (page 35, column 1 last sentence, bridging column 2, 1st paragraph). One would reasonably expect success because Bolger et al teach the success of the disclosed assay is a method for measuring competitive binding activity of molecules to steroid hormone receptors (page 4, lines 12-13).

Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bolger et al. (1998, WO 98/05962) in view of Roeder et al (2001, US Patent No. 6,248,520, filed 6 July 1998) and Burbaum et al (1999, US Patent No. 5,876,946) and further in view of Bhakta et al (1992, Arch Biochem Biophys 292:303-310). The teachings of Bolger et al. and the '520 and '946 patents are discussed above. Bolger et al do not a progesterone receptor (PR) wherein the K_d is 2.5 nM. Bhakta et al. teach an antisteroid

molecule ZK98299 that binds with high affinity (K_d of 2.5 nM) functional PR receptor in calf uterus cytosol (page 303, abstract). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to ultilize progesterone-like ligand that binds with high affinity to the PR receptor taught by Bhakta et al. in the method of measuring competitive binding activity of molecules to steroid hormone receptors taught by Bolger et al, including the fluorescently-labelled ligands disclosed by Burbaum et al in the reaction mixture. The person of ordinary skill in the art would have been motivated to make these modifications because Bhakta et al. teach the competitive binding between the antisteroid molecule ZK98299 and progestins (page 303, abstract) and Bolger et al teach that the disclosed assay is a method for measuring competitive binding activity of molecules to steroid hormone receptors (page 4, lines 12-13). One would reasonably expect success because Bolger et al teach the success of the disclosed assay is a method for measuring competitive binding activity of molecules to steroid hormone receptors (page 4, lines 12-13),

Objections

Claim(s) 26-29 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusions

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SHS

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER